



ANNEX I

Dynamic Culture Device User Requirements Form (PRELIMINARY DRAFT)

Scope of the document

Within the WP4 activity plan, a User Requirement Document is needed to start the design activity of Bioscent Dynamic Culture Devices; this document offers to Bioscent partners a list of requirements/issues related to the devices to be realised.

The present preliminary draft of the User Requirement Form in this version is offered to Bioscent partners in order to allow the definition of the final User Requirement Form: namely the following documents will be released:

- Dynamic Culture Device User Requirements Form (PRELIMINARY DRAFT)
- Dynamic Culture Device User Requirements Form
- Dynamic Culture Device User Requirements
- Dynamic Culture Device Specifications

Based upon these documents, the Dynamic Culture Device Architectural and Detailed Design Documents will be accordingly defined.

INSTRUCTIONS TO PARTNERS/USERS

Bioscent partners are requested to finalise this document by:

- adding/rephrasing/cancelling requirements
- adding/rephrasing/cancelling comments
- applying any further variation considered necessary/useful

Anyway, please consider that the most the User Requirement Form will be concise and unambiguous, the best the User Requirements document sorting out and the most effective the design activity.



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1. System content and scope

1.1 Scope of the system

(General information on system and software purpose)



1.2. Use case list

(Description of a system's behavior and detailed scenario-driven threads through functional requirements see chapter 2)



In the following charts the DCDs will be indicated with the following acronyms:

- Blood vessel Bioreactor: **BV**; - Heart Valve Bioreactor: **HV**; - Cardiac Patch Bioreactor: **CP**; - Cardiac Hydrogel Bioreactor: **CG**.

2. Functional requirements

2.1. Tissue type

Type of tissue the system should be able to grow; check the suitable box and express your comments

Tissue type	Bioreactor allocation			
	BV	HV	CP	CG
Cardiac muscle				
Heart valve				
Vascular tissue				
Other (Specify):				



2.2. Cell type

(Lines of cells the system is supposed to grow; check the suitable box on the left)

2.2.1. Human cells

Specify Lineage	Comments	Bioreactor allocation			
		BV	HV	CP	CG

2.2.2. Animal cell lines

Specify Lineage	Comments	Bioreactor allocation			
		BV	HV	CP	CG



2.3. Scaffold type

(Type of scaffold the system will support; check the box corresponding to the suitable bioreactor for each scaffold)

Material	Overall shape	Bioreactor Type			
		BV	HV	CP	CG
Scaffold 1:					
Scaffold 2:					
Scaffold 3:					
Scaffold 4:					
Scaffold 5:					
Scaffold 6:					
Scaffold 7:					
Scaffold 8:					



2.4. Stimulation and perfusion

Type of stimulation and perfusion required; check the suitable box and refer to paragraph 3 for details.

Stimulus	Comments	Bioreactor Type			
		BV	HV	CP	CG
Mechanical					
Electrical					
Fluidic					
Others (Specify):					

Culture media handling	Comments	Bioreactor Type			
		BV	HV	CP	CG
Seeding:					
- Static culture medium					
- Perfusion					
- Air/media interface					
Culture phase:					
- Static culture medium					
- Perfusion					



3. Performance requirements

3.1. Stimulation and culture medium

Insert details of the correspondent stimuli selected at paragraph 2.4; check the suitable box and express desired ranges and accuracies

Mechanical parameters	Range (\pm accuracy)			
	BV	HV	CP	CG
Peak force [N] <input type="checkbox"/> or Stress [MPa] <input type="checkbox"/>				
Max. Elongation [mm] <input type="checkbox"/> or Strain [%] <input type="checkbox"/>				
Frequency of stimulation (Hz):				
Other (specify):				

Electrical Parameter	Range (\pm accuracy)			
	BV	HV	CP	CG
Stimulation voltage [mV] <input type="checkbox"/> or Stimulation current [mA] <input type="checkbox"/>				
Other (specify):				

Perfusion parameters	Range (\pm accuracy)			
	BV	HV	CP	CG
Flow [mm ³ /s]				
Pressure [Pa]				
Other (specify):				



Other parameters (specify)	Range (\pm accuracy)			
	BV	HV	CP	CG

3.2. Measurement

Applicable measurement	Range (\pm accuracy)			
	BV	HV	CP	CG
Temperature				
Dissolved CO ₂ [Pa]				
Dissolved O ₂ [Pa]				
Glucose rate [mol/ml]				
Lactate Rate [mol/ml]				
Ammonia rate [mol/ml]				
Glutamine Rate [mol/ml]				
pH				
Other (specify):				

3.3. Sterilization

Parameters	Range (\pm accuracy)			
	BV	HV	CP	CG
Type of sterilization (Specify):				
Maximum temperature tolerable [°C]				
Maximum humidity [%]				
Maximum pressure tolerable [Pa]				
Other sterilization requirements (specify):				



4. Design, operational and control requirements

4.1. Layout

Parameter	Bioreactor Type			
	BV	HV	CP	CG
Number of constructs supportable				
Desired Handling (construct manipulation, mounting procedures, etc.):				
Spatial orientation of constructs (specify):				
Priming Volume (ml):				
Others (i.e. desired positioning of chemical sensors):				



4.2. Control & Monitoring / User interface

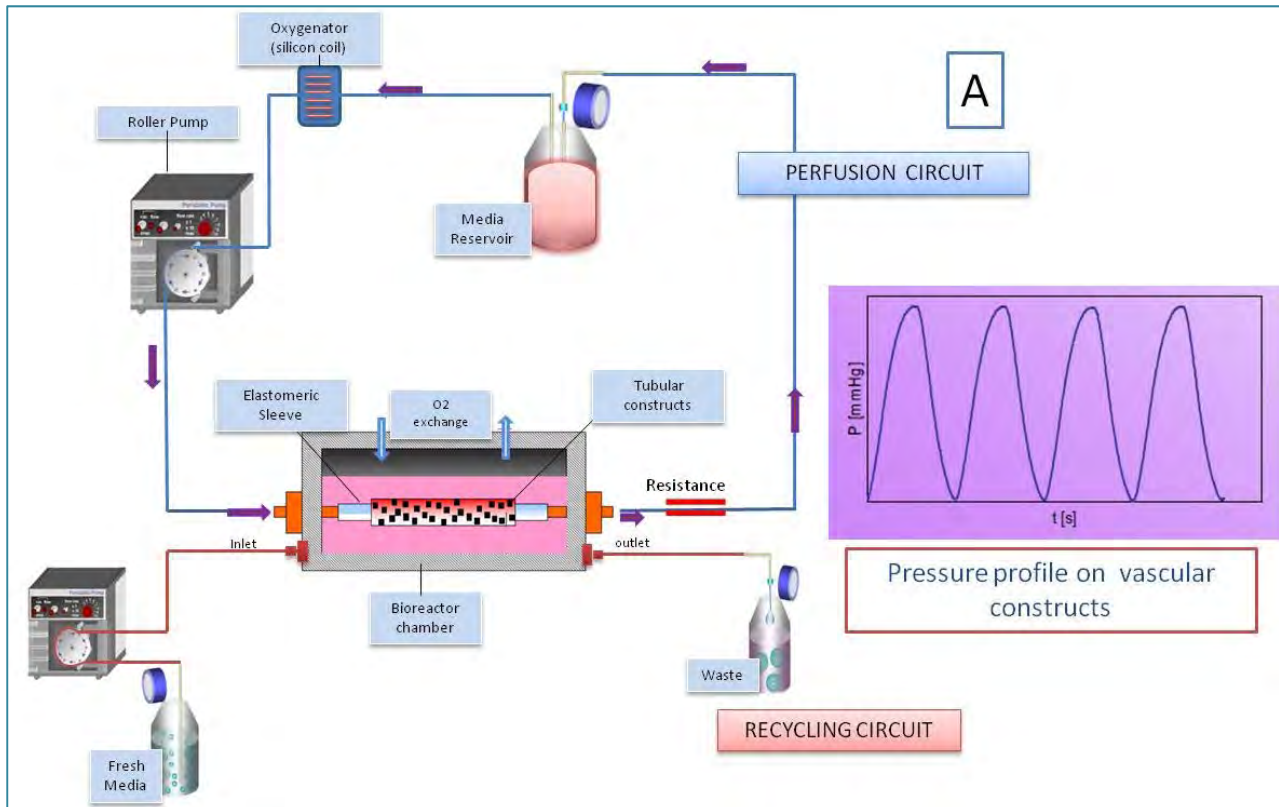
Check and comment the desired control of the stimulated samples within the bioreactor at the graphic interface

Parameter	Comments	Bioreactor Type			
		BV	HV	CP	CG
Displacement graphic control					
Load graphic control					
Others (Please provide suggestions / indications for the monitoring and controlling of the parameters)					

Annex: Possible DCDs architectures for Tissue Engineered Products

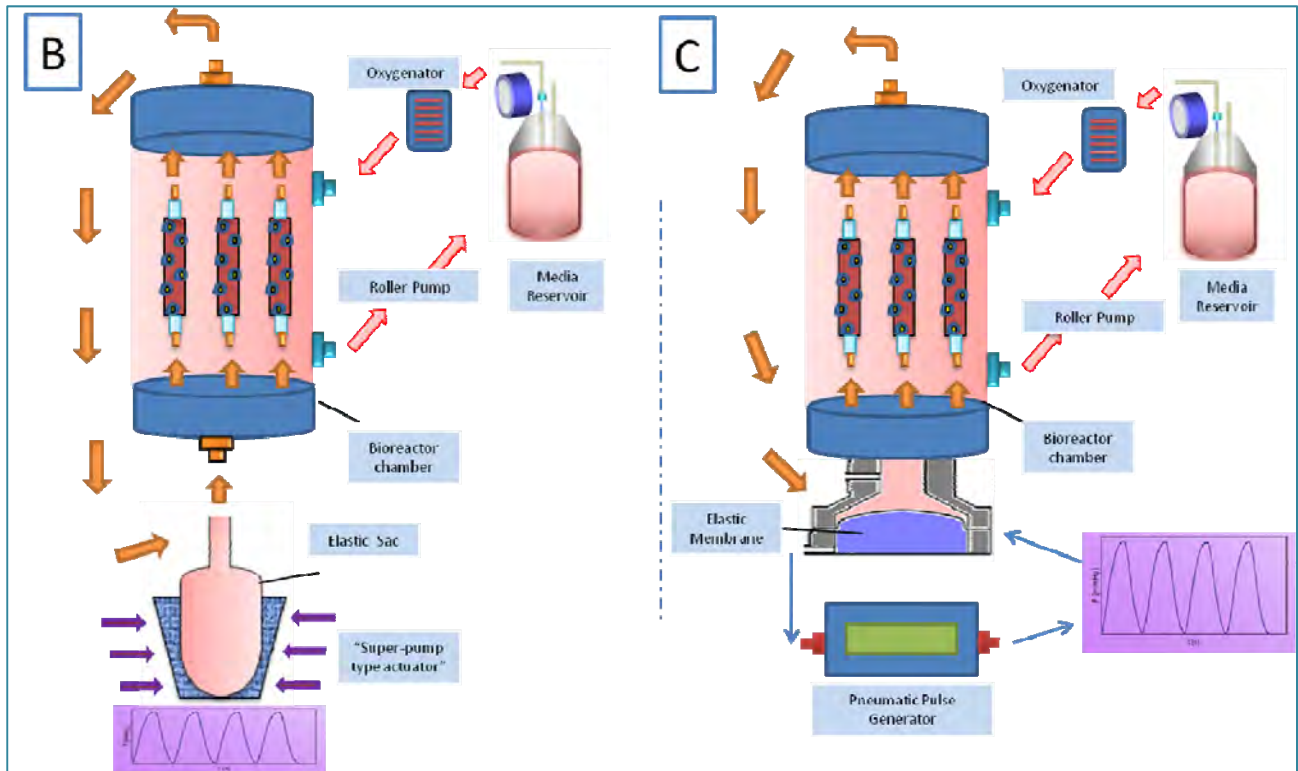
Annex I

-Bioreactor for blood vessel graft (BV)



- Possibility to use the Bioreactor chamber (or the primary circuit) for cell seeding.
- Physiological-like pressure within the vascular structure.
- Use of a roller pump and modulated RC circuit for the generation of pulsatile regimen of radial strain and shear stress (variation of the compliance/resistance/pinch valve configuration allows to vary phase relationship between pressure and flow through the graft).
- Media recycling inside the bioreactor chamber might be obtained through a second peristaltic pump (or a independent circuit operated by the same pump).
- Use of fresh oxygenated media to nourish the construct while stimulating.

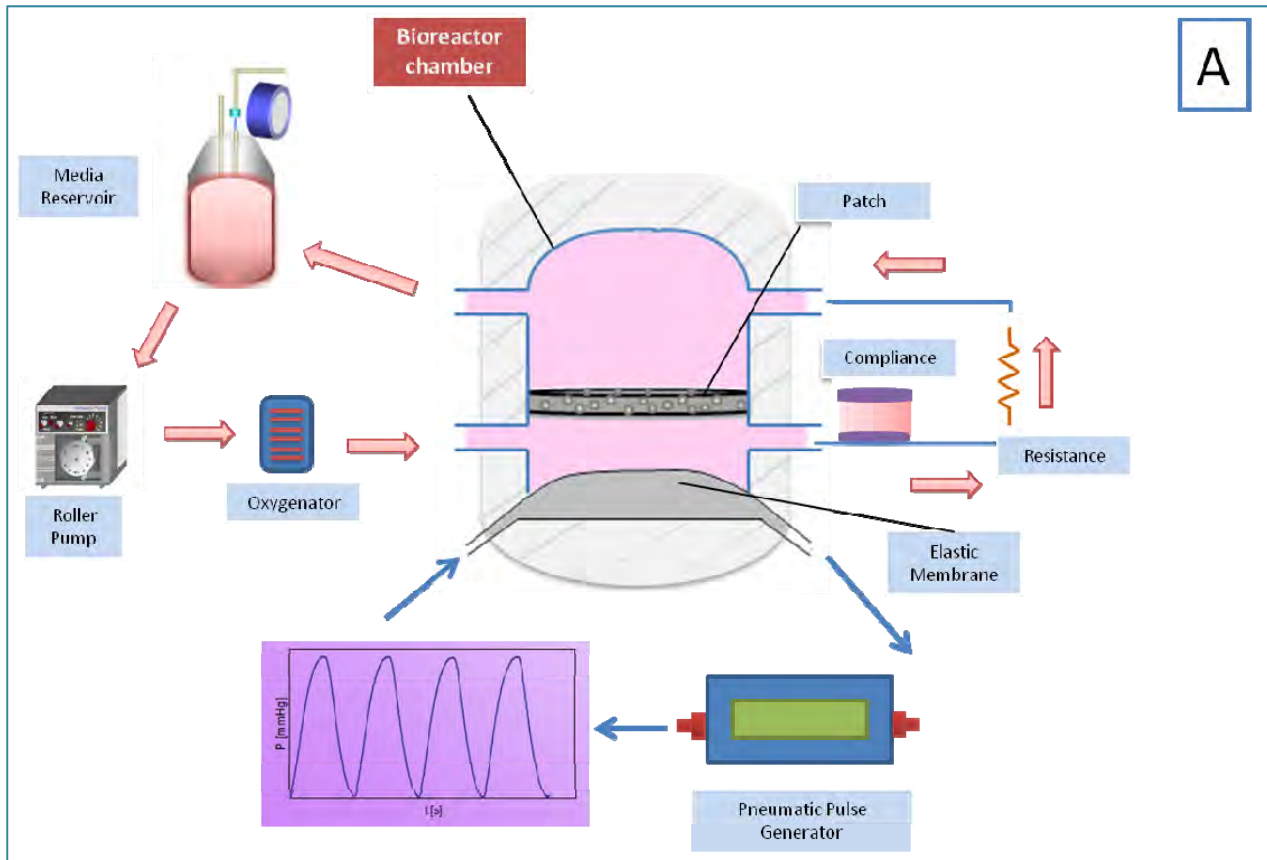
-Bioreactor for blood vessel graft (BV)



- Physiological-like radial pressure within the vascular structure.
- Hydraulic actuator and flexible sac (same type as “Superpump” pulse duplicator) (B) or pneumatic actuator with elastic rubber membrane for the generation of pulsatile regimen of strain and shear stress (C).
- Automated media recycling inside the bioreactor chamber through a peristaltic pump.
- Use of fresh oxygenated media to nourish the construct while stimulating.
- Possibility to use multiple smaller cartridges to reduce priming volume, consumption of media and for cell seeding.

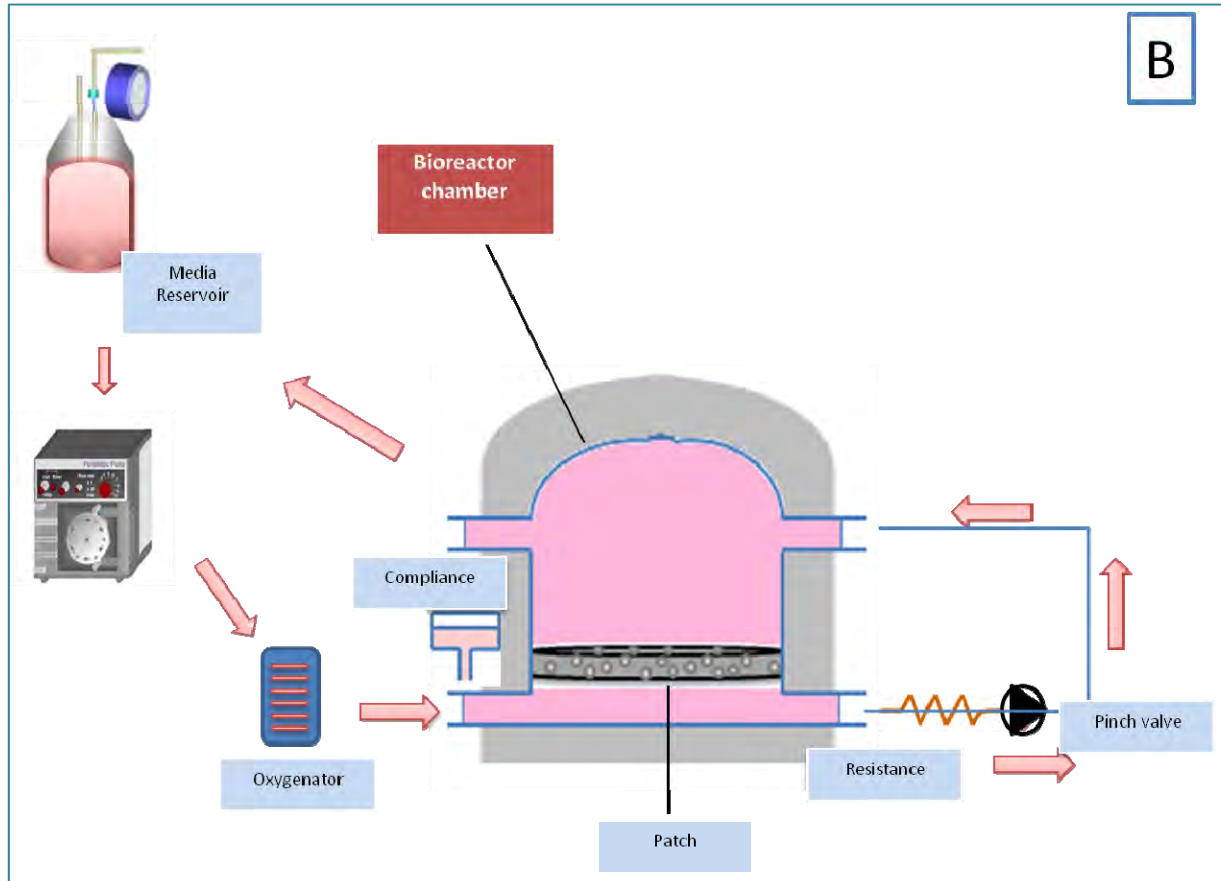
Annex II

-Bioreactor for Cardiac Patch (CP)



- Use of a roller pump to circulate fresh feeding media inside the bioreactor chamber and a modulated RC circuit to mimic the stress/relaxation cycles of the heart.
- Generation of a physiological-like pulsatile pressure on the constructs.
- Use of fresh oxygenated media to nourish the construct while stimulating.

-Bioreactor for Cardiac Patch (CP)

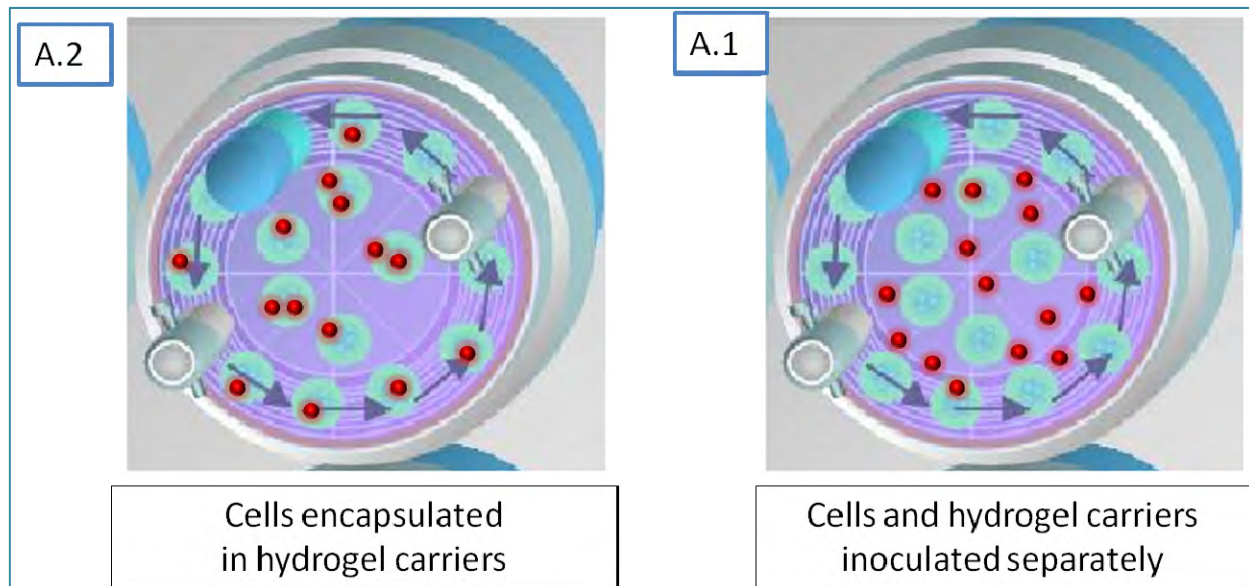


- Use of a roller pump to circulate fresh feeding media inside the bioreactor chamber and a modulated RC circuit to mimic the stress/relaxation cycles of the heart
- Generation of a physiological-like pulsatile pressure on the constructs
- Use of fresh oxygenated media to nourish the construct while stimulating

Annex III

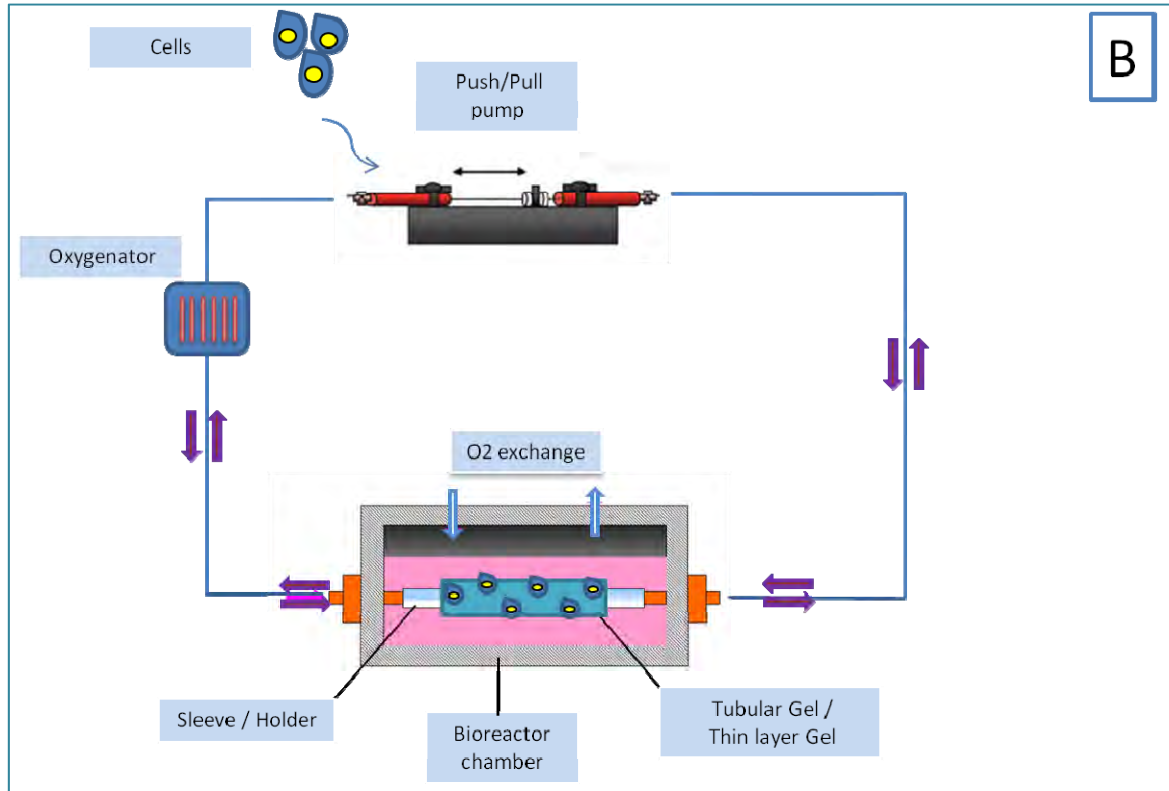
-Bioreactor for hydrogels in cardiac application (CG)

- Rotating bioreactor for hydrogel cell recruitment



- Rotating culture bioreactors (RCBs) combine high mass transport rates with very low shear force (1 dyne/cm^2), in conjunction with predominately laminar flow conditions.
- RCBs can be used to culture cells to assess the ability of the implemented gel to favor cell bioprocessing
- Cell can be directly encapsulated within gel micro carriers to evaluate cell growth/ differentiation (A.2)
- Alternatively gel carriers and cells can be transferred separately in the RCBs to evaluate the gel ability to recruit cells in the environment and to further promote growth/ differentiation (A.1)

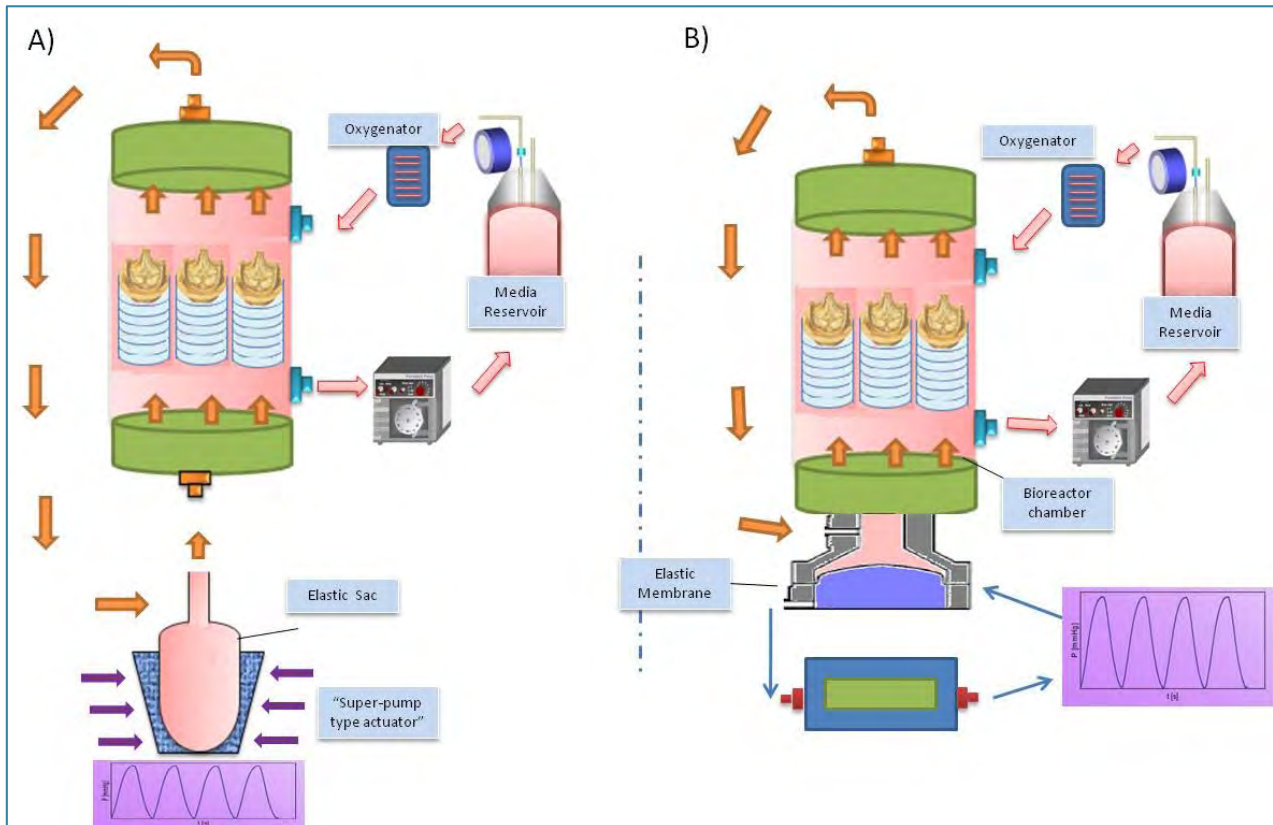
- Bioreactor for hydrogel cell seeding & recruitment



- The hydrogels may be casted in form of tubules or thin film to test cell recruitment capability and enhance the generation of functional tissue-like structures
- Use of a push-pull pump to seed cells
- The perfusion circuit could be implemented as well with a roller pump

Annex IV

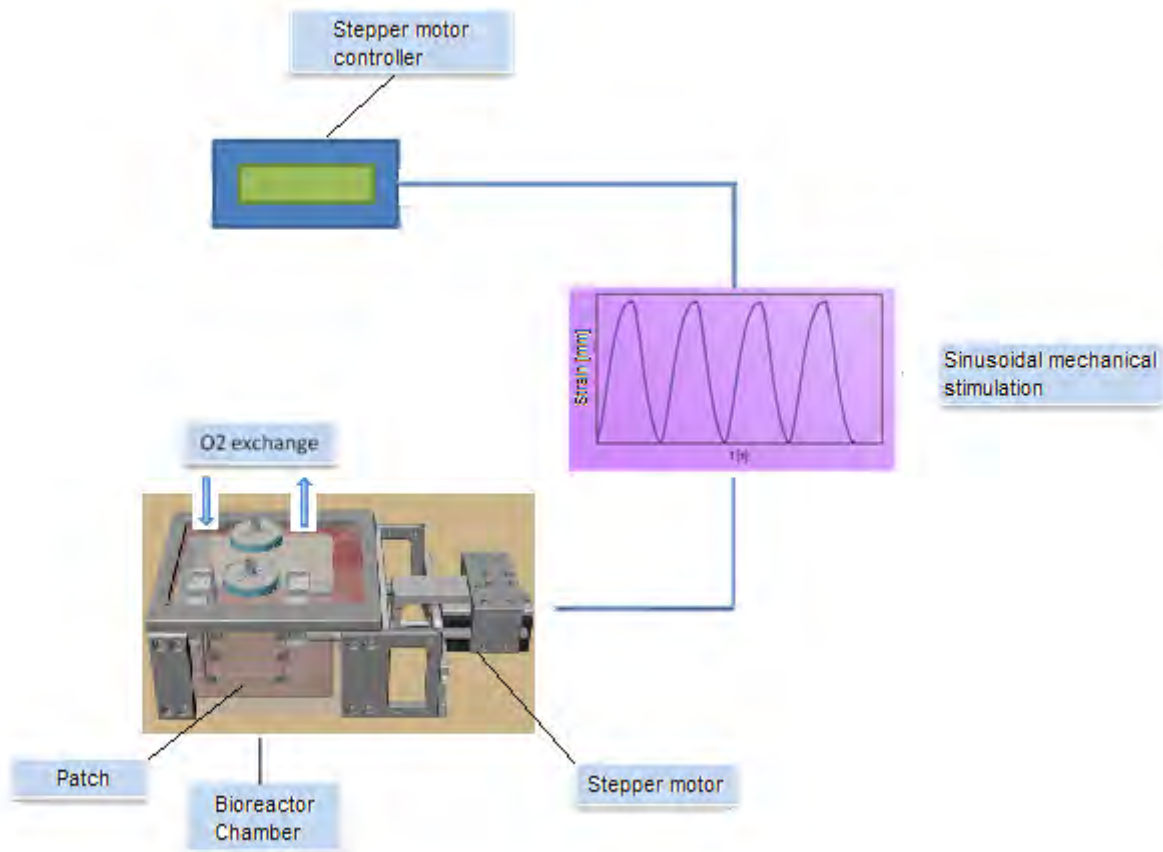
- Heart valve Bioreactor (HV)



- Pulsatile flow through the heart valve construct
- Hydraulic actuator and flexible sac (same type as “Superpump” pulse duplicator) (A) or pneumatic actuator with elastic rubber membrane for the generation of pulsatile regimen of strain and shear stress (B).
- Automated fresh media recycling inside the bioreactor chamber through a peristaltic pump.
- Use of fresh oxygenated media to nourish the construct while stimulating.
- Possibility to use multiple smaller cartridges to reduce priming volume, consumption of media and for cell seeding.

Annex V

- Mechanical Bioreactor



- Use of a stepper motor to stretch the patch.
- Generation of a sinusoidal stretching pattern.

ANNEX II - BUSINESS MODEL

Channels

In order to reach its customers and targets, Biomicron CED's marketing strategies will envisage public relations, articles in specialised magazines, technical workshops, seminars, scientific congresses, public meetings and promotions with both research centres and hospitals. A website will also be created to publicise the business activity and a campaign of direct contacts with the research centre and hospital laboratories is envisaged, all with the main aim of developing awareness of the products and knowledge of the company. All the activities following production (purchase, delivery, after-sales service) will initially be pursued through direct contacts between the staff of Biomicron CED and customers.

Customer Relationship

The company intends to offer direct personal service to buyers, in keeping with the aim of setting up a stable relationship with them. In particular, the idea is to offer a more effective after-sales service than the competition, installing the product at the buyer's premises, training staff in the use of the device and withdrawal/exchange of the used product.

Customer Segment

Adapting its methods and timing, the company intends to approach two main market segments: hospitals and research structures, considering the second category to be an articulated combination of red biotech companies, research centres and IRCCS (Institute of Scientific Recovery and Care).

Revenues

Biomicron CED's main revenue stream comes from the direct sale of its product to the end customer. The royalties from the sale of specific disposables will represent a source of parallel revenues capable also of encouraging the continuity of a relationship (indirect) with the customer. The company also intends to offer its technical know-how for the planning of upgrades or new bio-reactors to suit customer requirements. This activity, which was initially performed by entrepreneurs, will generate revenues in the form of technical consulting in relation to the products.

Key Resources

The first fundamental resource identified consists of the specific capacities of the design, assembly, maintenance and servicing staff. The skills of staff must be suited to the construction of a product like the bio-reactor, and must therefore combine sensitivity towards medical-clinical issues and technical skills. A second key resource will be intellectual property, given that every effort will be made to protect some of the technical solution with patents.

Key Activities

The future company will concentrate on the phases of concept/design of the product in all its components (main and accessory) and on those of product marketing. Other activities central to the

business strategy will be assembly (which for a product as innovative as that in question is a critical and complex activity) and after-sales assistance for customers.

Key Partners

The company will make use of a fundamental cooperation with Biomicron Srl, which also cover the financier of the start-up, holding part of the company shares. This partner will take care of production and the complementary procurement activity, offering useful references for marketing, as well as legal and accounting aspects. The suppliers of the other components (actuators, sensors, etc.) will however be fundamental to ensure that the product conforms to market requirements.

Cost Structure

The company's cost structure will be initially centred on variable costs, i.e.: the costs linked to the production of the bioreactor, trying to reduce sunk costs which could limit the company's flexibility and worsen the initial lack of available funds. This cost saving activity will be accomplished thanks to cooperation with Turin Polytechnic, which will offer the premises to house the activity, at a commercial price, and to the partner Biomicron Srl which will offer the same service from the fourth year onward.

Value Proposition

The Biomicron CED proposition intends to match technological innovation and a competitive price. The first component in particular will be embodied by a device that simplifies the job of the operators, automate the processes, improve the quality of the results and guarantee very flexible use. Vice versa, the reduced cost will allow access to the technology in question to those organisations that are interested but have limited budgets. Lastly, the company would also like to propose its services as supplier of addition assistance and consulting.

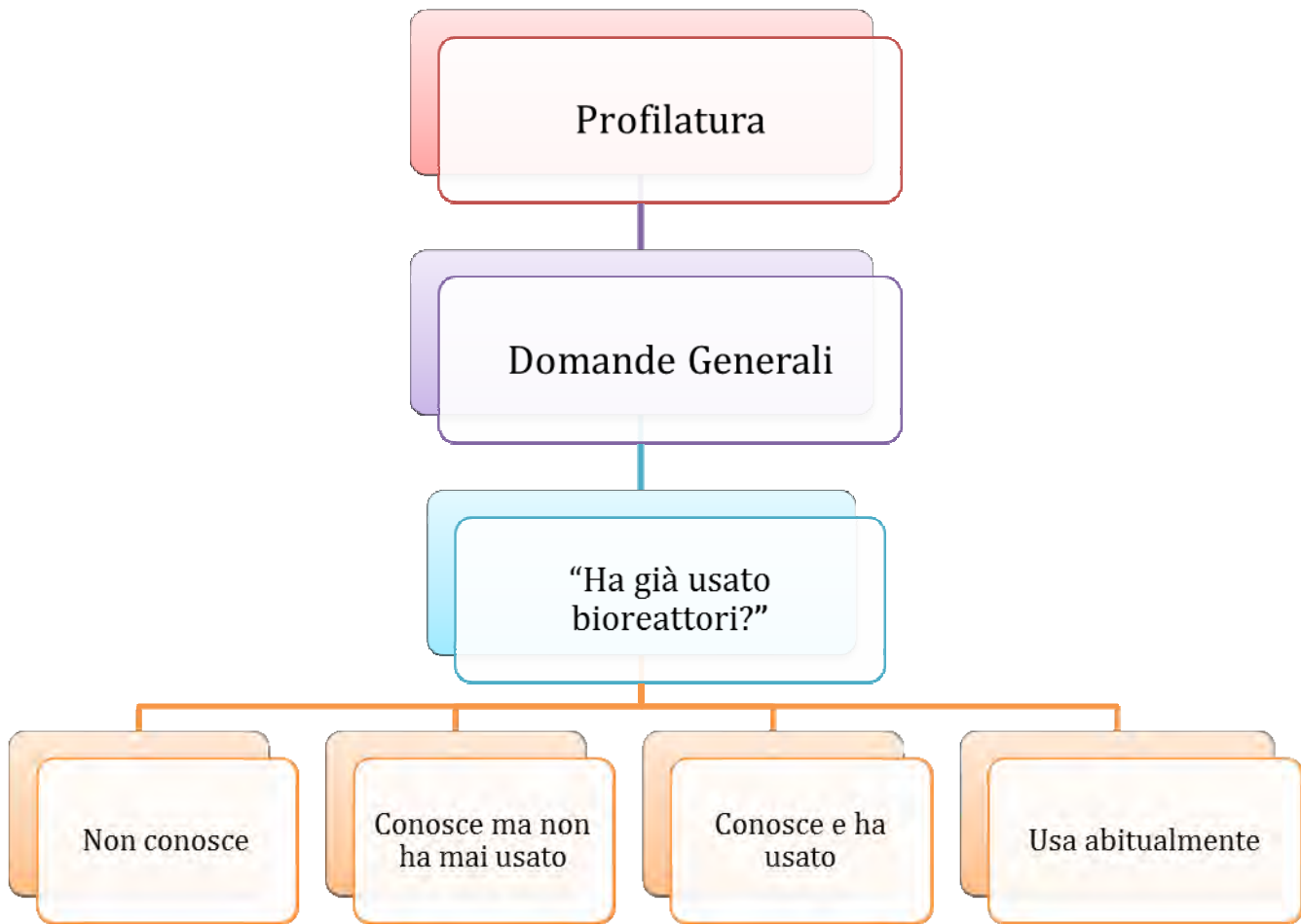
ANNEX III - Value proposition

TECHNOLOGY	FUNCTIONAL FEATURES	BENEFITS	
		USER (*)	NON-USER (*)
LVDT linear actuators capable of reaching high power and speed	Process automation and increased quality standards	Better results and time saving to perform experiments on different tissues.	
Systems for grafting and ungrafting the culture chamber from the other components	Bioreactor capable of using several types of tissue Multi-chamber	Reduction of purchase costs (10-50%)	Reduction of time to result
Use of disposables for some components	Reduction of the risks of contamination	Fewer experiments	Fewer experiments and more reliable results
Electronics for checking parameters and processes in a closed loop through dedicated circuits on microchip	Process automation and increased quality standards	Less operator stress and fewer human errors	
Control Logic based on the LabView® commercial platform	Simple, customised software package.	Better understanding of the results and easy use by users with less experience.	
	Possibility to manage the culture parameters automatically, using software, without intervening directly in the culture chamber.	Time savings (better with automatic management), reduced contamination risks, use by users with less experience.	

(*) the term user refers to a customer who, in his business activity, has already used a bioreactor and decides to purchase a Biomicon CED bioreactor; vice versa, the term non-user refers to a customer who has never used a bioreactor and decides to try one, the Biomicon CED product being his first choice.

ANNEX IV – Analysis of questionnaires

The questionnaires sent have the following structure:



- Profiling
- General Questions
- “Have you already used bioreactors?”
- I know about them
- I know about them but have never used them
- I know about them and have used them
- I use them regularly

The answers received are listed below:

Structure of origin			Percentage
	Private Research Centre	2	11%
	Hospital Structure	1	5%
	University	13	68%
	Public Research Public	3	16%

Professional Role			Percentage
	Researcher-teacher	1	5%
	Biologist	6	32%

Bioengineer	2	11%
Research Doctor	3	16%
Biotechnologist	3	16%
Immunologist	3	16%
Biochemist	1	5%

Sterilisation methods	Percentage
Steam autoclave	18 95%
Etox	1 5%
UV Ray	7 37%
Dry sterilisation	5 26%
Gamma rays	1 5%

Budget	Percentage
< 50,000	6 32%
50,000-500,000	1 5%
50,000-300,000	10 53%
> 1000000	1 5%
Don't know	1 5%

Cells used	Percentage
animals	16 84%
human	15 79%

Importance of the risk of contamination

	high	medium	low
Insemination phase	5	6	8

	high	medium	low
Culture phase	2	6	11

	high	medium	low
Extraction phase	5	8	6

Number of tissues used	Percentage
Only 1	3 16%
From 2 to 5	12 63%
More than 5	4 21%

Percentage of cultures carried out parallel	Number of Responses
0%	5

	10%	1
	20%	1
	30%	2
	35%	1
	40%	2
	50%	2
	60%	
	70%	1
	75%	1
	80%	2
	90%	1
	100%	

In the last 5 years, tissue types used		Percentage
Cardiac	3	16%
Bone	8	42%
Nerve	4	21%
Cartilage	1	5%
Vascular	4	21%
Epithelial	6	33%
Tumour cell plasma	1	5%
Embryonic	1	5%
Muscle	3	16%
Ovarian-testicular	1	5%
Stem cells	1	5%
Circulating lymphocytes	1	5%
Skeletal muscle	1	5%

Structure with a bioreactor		Percentage
yes	8	42%
no	11	58%

Link with the bioreactor		Percentage
<i>Known and used</i>	7	37%
<i>Known but not used</i>	9	47%
<i>Unknown</i>	3	16%

Interest in customised software		Percentage
yes	5	71%
no	2	29%

Additional services for those who use a bioreactor

	Have it and am interested	Don't have it but am interested	Not interested
Installation and staff training	5	2	0

	Have it and am interested	Don't have it but am interested	Not interested
Phone/online assistance	3	3	1

	Have it and am interested	Don't have it but am interested	Not interested
Maintenance and customised assistance	3	4	0

	Have it and am interested	Don't have it but am interested	Not interested
Exchange and withdrawal of used product	2	4	1

Functional importance for those who know and use the bioreactor

	Fundamental	Very important	Quite important	Not very important	Not important
Administration	1	3	3	1	0

	Fundamental	Very important	Quite important	Not very important	Not important
Automation	0	4	4	0	0

	Fundamental	Very important	Quite important	Not very important	Not important
Monitoring	2	4	2	0	0

ANNEX V - Competitors mapping

Biomicon CED product technology	Functional feature	Bose	TGT	Zellwerk	Biotoools
Components capable of reaching high power and high speed	Ease of use and customisation				
Systems for grafting and ungrafting the culture chamber from the other components	Multi-tissue Bioreactor			n/a	
Use of disposables for some components	Reduction of the risk of contamination				
Electronics for checking parameters	Ease of use and customisation				
External incubator unnecessary	Versatility	✓		✓	✓
High versatility (adaptability to tissues suitable for cultivation in traction and compression)	Versatility			n/a	
Easy scalability (expendable up to 12 chamber cultures)	Versatility		✓		
Access to the culture chamber from above (easy access)	Ease of use		✓	✓	✓
Optic access for phase contrast microscope	Versatility				
Easy opening and closing of the chamber without the use of instruments	Ease of use	✓	✓		✓
Possibility to install the samples outside the culture chamber	Versatility		✓	n/a	✓
High frequency mechanical stimulation	Versatility			n/a	
Peak force above 600N	Versatility			n/a	
Maximum force during culture cycles up to 400N	Versatility			n/a	
Maximum amplitude of mechanical stimulation up to 5 mm	Versatility			n/a	
Adjustment of the perfusion capacity	Versatility	✓	✓	✓	✓
Adjustments of the perfusion capacity on a broad range (from 0.1mL/min to 500mL/min)	Versatility				
Possibility for electrical stimulation	Versatility				

Gas expansion module to minimise air bubbles in culture fluid	Versatility		
User interface in a single window	Ease of use	✓	✓
Automatic management of the culture from insemination to removal	Ease of use		

Note: "n/a" stands for "not available"

ANNEX VI - Industry assessment

Internal rivalry

- Number of companies: currently 19; these include 3 major brands (Bose ElectroForce, TGT and Synthecon).
- Reputation (brand identity): Bose ElectroForce is a consolidated and well known brand. The other competitors, while not yet having a solid reputation, have good possibilities of this becoming consolidated in the future.
- Switching costs for buyers (product): there are no relevant switching costs, because for other instruments linked to the use of bioreactors, such as incubators, scaffolds and laboratory instruments are not restricted to the model in use. The switching costs will tend to rise insofar as there will be greater attention paid to connected services. Internal rivalry will decrease.
- Exit barriers: The facilities aren't dedicated solely to the production of bioreactors, but can also be used for other purposes (there are no high costs for conversion of the production facilities). This means that there are no large exit barriers.
- Product standardisation: different tissues correspond to different products; all the other features such as single chamber/multi-chamber, disposable/non-disposable, modular/non-modular, etc... mean that the product is differentiated. This is confirmed by the absence of a dominant bioreactor design. Furthermore, it is a product purchased by those specialised in the sector, who don't see it as a standard product.
- Transaction frequency: the average life of a bioreactor is about 4-5 years.
- Informative complexity of the transactions: complex transactions, even when carried out by specialised buyers who reduce the informative asymmetry. Moreover, the specific features of the bioreactor and the production process aren't all that clear, not even to experts.
- Growth rate in the sector: the biotechnologies sector, particularly red biotech, is growing mainly in Europe and the emerging countries. The growth rate is 5-6% in Europe and 15% in the emerging countries.

GLOBAL JUDGEMENT – Internal rivalry: AVERAGE

Entry barriers:

- Economies of scale: current production volumes are low and bioreactors are not standard products, so there are no big economies of scale. There could be greater economies of scale in the production of disposables.
- Economies of scope: medium-low economies of scope, because in adjacent sectors the products of incubators, centrifuges, fermenters, etc., which do not fully share the same machinery and the same skills, are considered.
- Difficulty in accessing human resources: professional figures in the biomedical field who have matured specific know-how and experience in the bioreactor sector are not easy to find, as they combine technological and design aspects with biological knowledge.

- Control of businesses in the sector operating in raw materials and distribution channels: as the market guarantees and extensive offer and free access to raw materials and the components required for the production of bioreactors, there is no difficulty in finding them. As regards distribution channels, however, there could be greater complications with access to certain foreign markets, particularly the emerging markets.
- Economies of learning: the production of bioreactors is complex to achieve because it requires both technical skills and sensitivity towards the field of biotechnologies and the relative problems. Consequently, it is a “learn-by-doing” and this creates a considerably barrier towards entry.
- External positioning of networks: these do not create a barrier because external positioning is very infrequent. This is justified by the fact that the purchase of a bioreactor by a user does not encourage another user to purchase it and the value perceived by the buyer is generated entirely by the intrinsic value of the product. There is no need to reach a critical mass and at the moment there are no consolidated technological standards.
- Presence of intellectual property: patents are an obstacle to entry, insofar as they are multiple, both in relation to product and process.
- Brand loyalty: the judgement is consequential to that claimed with regard to switching costs and in relation to the importance of services (after-sales service, maintenance, etc.) in creating brand loyalty.
- Government and legal barriers: there is no need for government permits to produce bioreactors.
- Threat of retaliation by competitors (incumbent): in the short term, the main threat will be linked to spin-offs similar to Biomicron CED; while in the long term, it is thought that the main obstacles will be created by consolidated competitors.

GLOBAL JUDGMENT – Entry barriers: MEDIUM-LOW

Power of suppliers

- Number of suppliers: the raw materials purchased by those who produce bioreactors are commodities that can easily be found by a large number of suppliers; the same goes for components such as pumps, sensors and linear actuators, despite these being more specific for bioreactors. Even where the percentage of purchases from the same supplier is considerable, there is an awareness by the customer and the supplier of the wide variety of rival suppliers who can guarantee the same resources.
- Differentiation of supplier product: in general, all the input used is quite standard and undifferentiated, although sensors and certain more specific components can present major peculiarities that lead to a “medium-low” rather than “low” judgement.
- Switching costs for the producers of bioreactors: these costs are low but not non-existent, insofar as there can be early terminations of contracts and diseconomies linked to the fact that the new supplier might not agree to the same conditions and discounts.
- Threat of subsequent integrations: the threat of integration of suppliers is unlikely and therefore of little importance.
- Cost saving deriving from the purchase of components from specific suppliers: in general, the low differentiation of the components used implicates a low differentiation of price, which translates into lower potential savings in passing from one supplier to another.

- Importance of the quality of the components of specific suppliers: the quality of the components is in actual fact important, but there isn't much difference in quality between suppliers. Consequently, the impact of this factor is limited in the judgement on the power of suppliers.
- Cost of the components of suppliers in relation to the total cost of producers: the main cost categories are: research and development, production, marketing and any accessory after-sale costs. Despite not being negligible, the cost of certain specific components in relation to the production cost, their weight in relation to the total cost is limited, reducing the power of the suppliers.

GLOBAL JUDGMENT – Power of suppliers: LOW.

Power of Customers

- Threat of integrations: the threat of integration of customers is unlikely and therefore of little importance. As stated earlier, the production of a bioreactor is complex because it requires technical skills and sensitivity, particularly in terms of mechanical design, and these skills are not possessed by biology experts.
- Switching costs for customers: there are no relevant switching costs, because other instruments connected to the use of bioreactors, such as incubators, scaffolds and laboratory instruments are not restricted to the model in use.
- Volume of purchase by the same customer: it is more likely that there will be a large number of customers who buy just a few bioreactors at a time than a small number of customers who buy lots of bioreactors.
- Differentiation of manufacturer product: different tissues correspond to different products; all the other features such as single chamber/multi-chamber, disposable/non-disposable, modular/non-modular, etc... mean that the product is differentiated. This is confirmed by the absence of a dominant bioreactor design. Furthermore, it is a product purchased by those specialised in the sector, who don't see it as a standard product.

GLOBAL JUDGMENT – Power of customers: AVERAGE.

Substitute products

Bioreactors can be replaced by the traditional in vitro cell culture.

If we consider the use of bioreactors also for transplants, then the traditional transplant and artificial products (e.g.: heart valves, etc.) are also potential substitutes.

To calculate the level of suitability as a substitute, the current and future situations in terms of bioreactor market development were taken into account:

Present:

1. MEDIUM-HIGH substitution of in vitro cell culture, because bioreactors are an “evolution” for specific needs with respect to traditional culture;
2. LOW substitution of in vivo cell culture, because the tests cannot be carried out on people (in vivo culture envisages the development of the tissue directly on people).

Future:

1. LOW substitution of in vitro cell culture, because the latter is not very well suited to this type of use;
2. HIGH substitution of in vivo cell culture, because both develop tissues destined for transplant, with the difference of the extension of the tissue outside or inside the body. While suitability for substitution increases, the complementary aspects also increase, because bioreactors would be used to carry out in vivo pre-transplant tests and for parallel monitoring.

Generally-speaking (based upon research carried out and questionnaires analysed) we can conclude that many researchers would be interested in working in the field of regenerative medicine with bioreactors, because they allow more automated culture which reduces human intervention in certain phases and, consequently, the risk of human error and contamination. The only variable that influences the rate of substitution is the price of the bioreactor.

GLOBAL JUDGEMENT – Substitute products: MEDIUM-LOW.

ANNEX VII – Gantt of activities

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	60			
R&D ACTIVITY																																									
COMPANY INCORPORATION																																									
TESTER IDENTIFICATION																																									
FIRST PRODUCT DEVELOPMENT																																									
					FINAL IN-HOUSE TESTING																																				
						PATENTING (FOR 2-3 YEARS)																																			
						OUTSIDE TESTING																																			
													PRODUCT RE-ENGINEERING																												
																		PRODUCT CERTIFICATION																							
	ECONOMIC-FINANCIAL ACTIVITY																																								
																		PRODUCTION PROCESS PLANNING																							
																		COMPONENT SUPPLIER IDENTIFICATION																							
																		MARKETING ACTIVITIES (INCLUDING PLANNING OF SALES PROCESS UNTIL THE 23 RD MONTH)																							
																		FIRST CUSTOMER IDENTIFICATION																							
																		WEBSITE CREATION																							
																					PRODUCTION PROCESS IMPLEMENTATION																				
																						PRODUCTION PROCESS IMPLEMENTATION																			
																											ATTIVITA' DI PRODUZIONE														
																											ATTIVITA' DI COMMERCIALIZZAZIONE														
																											ATTIVITA' DI GESTIONE POST-VENDITA & ASSISTENZA														

ANNEX VIII - Implementation Plan

Prototyping phase

ACTIVITY	PERIOD	RESOURCES
Incorporation of the company with the cooperation of Biomicron Srl which will hold 30% of the company	1 st month	Notary, entrepreneurs, funding
Identify tester	1 st month	Entrepreneurs, list of contacts of experts-acquaintances, phone, PC
R&D activity	From 1 st month onwards	Funding, PC, experts
First product development	From 1 st to 6 th month	Entrepreneurs, special instruments, software, funding, PC
Economic-financial activity	From 2 nd month onwards	PC, analyst, billing of accounts
Final in-house testing	6 th month	Entrepreneurs, experts in the sector, software (scaffold samples)
Patenting	From 7 th month onwards	Patents office, entrepreneurs, product validity control software
Outside testing	From 7 th to 15 th month	Expert in the sector, adequate environment, PC
Product re-engineering	From 14 th to 18 th month	Entrepreneurs, special instruments, software, funding, PC

Industrialisation phase

ACTIVITY	PERIOD	RESOURCES
Product certification	From 19 th to 21 st month	Funding, premises for product certification and control, experts, entrepreneurs
Production process planning	From 19 th to 21 st month	Experts in the sector (Biomicron Srl), PC, suppliers, Biomicron Srl
Identification of component suppliers	From 19 th to 21 st month	Entrepreneurs, PC, telephone

Planning of sale process	From 19 th to 23 rd month	Spin-off components , PC, Biomicron Srl
Identification of first customers	From 19 th to 26 th month	Entrepreneurs, Biomicron Srl, PC, telephone
Website creation	19 th month	IT experts, funding
Implementation of production process	From 22 nd to 25 th month	Funding, expert in the sector (Biomicron Srl)
Implementation of sale process	From 24 th to 26 th month	Funding, spin-off components

Production phase

ACTIVITY	PERIOD	RESOURCES
Marketing activity	From 27 th onwards	Experts in the sector, trucks, distributors, packaging staff, special instruments, PC, labour, labelling instruments
Production activity	From 27 th onwards	Funding, suppliers, PC, entrepreneurs, special instruments, labour, adequate environment
Management of after-sale activity and assistance	From 27 th onwards	Entrepreneurs, PC, software, user manuals, special instruments, spare instruments, technicians

ANNEX IX – Timing of entry onto the market

To observe the entry aims, the strategic activities to be implemented are:

<u>SHORT-term aims</u>	<u>MID-term aims</u>	<u>LONG-term aims</u>
Communicate the product (the VP) to a certain number of potential Italian customers to create the first future contacts.	Growth of product awareness among potential customers in Italy and abroad.	Creation of brand awareness

Short Term: during this period of time, the company proposes to communicate and publicise its value proposition to potential future customers. The main activity will be to create the first contacts with future buyers to show the innovation related to the product and to reassure them of the quality of the bioreactor and of the company.

Mid-Long Term: having begun the product industrialisation phase, the company will have to continue investing considerable resources to further increase customer awareness, and other resources will be necessary to develop technological innovation in such a way as to maintain distance from competitors. Product awareness is vital for a company which has just entered the market, much more so than brand awareness to which the company will dedicate resources later. Biomicron CED will focus its resources on a specific model of product (bioreactor for cardiovascular tissue) and only later will it expand its range of products with new models.

Long Term: the company will invest its resources in brand awareness and, above all, in what is described as “brand quality”. The main aim of the entrepreneurs is to make the name Biomicron CED synonymous with the product and the reliability of the results, insofar as it will be used in the biomedical sphere. A second aim will be that of transforming a push type distribution strategy into a pull type strategy, meaning that Biomicron CED will have to exploit previous investments to expand its contacts with customers and for development of the brand, so that the end customer will contact the company and not vice versa. A third aim will be to create new product models for different tissues, in order to differentiate the product and expand market demand.

In general, we need to remember that the characteristics of the high technology sector in question lead to the consideration of the brand identity factor as relatively unimportant, in the short term, when it is possible that the characteristics of the product may carry more weight than the brand. Vice versa, looking at things in the long term, the company could imagine being able to “induce” brand identity in a market where, at the moment, it seems to have little influence, acting as provider of services and creating customer loyalty by proposing a direct assistance relationship.

ANNEX X – SWOT Analysis

► **S-O Strategies:**

- Exploit the experience and consolidated know-how of entrepreneurs, the high technological content and the extensive offer of services, to focus the strategy of satisfying the needs of users, filling the gap between demand and supply.

For example, the sale could be accompanied by the disbursement of cell culture assistance or product customisation options could be offered to suit requirements.

- Speed up the growth of the company on the market, exploiting the partnership with Biomicron Srl and the absence of a dominant design.
- Increase communication, emphasising the good price-quality ratio and the positioning as a niche product, to tackle the albeit limited number of competitors who are already consolidated. (e.g.: presence at trade fairs, announcements in specialised magazines, on websites, etc.).

► **S-T Strategies:**

- Patent Biomicron CED solutions and technologies with the aim of protecting them from any substitute technologies by competitors already consolidated on the market.
- Exploit the partnership with Biomicron Srl, cooperating in sourcing key resources and implementing a raw material cost sharing policy.
- Exploit in-house assembly to develop more control over the finished product, checking its distribution and inimitability by competitors.
- Participation as shareholder of Biomicron Srl to mitigate the risks deriving from the presence of a single supplier for ad hoc components.

► **W-O Strategies:**

- Exploit the vicinity with the academic world and set up further cooperations with special structures for start-up (university incubators), trying to source research funds to cover the initial investments in R&D.
- Implement policies aimed at maintaining lasting relationships with customers, to obtain a broad basin of loyal customers with a desire to cooperate. In this way it is possible to speed up entry to market and the relative time to market, also making up for the lack of knowledge of the business world by entrepreneurs.

► **W-T Strategies:**

- Reduce the time to market to cope with the development of substitute technologies and imitations by competitors (advantage of quick implementation in research centres). For example, if the product is introduced quickly into research centres, scientists will study and operate exclusively on Biomicron bioreactors, with a consequent very high switch-off cost to rival technologies.
- Activate several partnerships and outside cooperations (with Biomicron Srl, University research centres, etc.), to make up for the lack of knowledge of the business world and have more funds to cope with the risk of increased costs and high initial investments.

ANNEX XI - Marketing and selling plan

Customer acquisition process

Phases/activities	Operating levers	Activities and resources
Sourcing of suppliers/manufacturers	Customer must know Biomicron CED as a supplier of bioreactors	Promotional activities described in the business plan
Request for information/estimate	Publicise products, prompt response to requests for information or an estimate	Commercial operators and planners available also on secondment and capable of quickly meeting the needs of customers. Technical skills, informative brochures
Evaluations of estimates/screening of bids	Remain at the customer’s disposal to provide any additional information	Commercial operators and planners available
(Request for demo + demo)	Need for a functioning product available on trial	Planner + commercial operator Prototype, means of transport, PC and software
Final assessment and choice	Remain at the customer’s disposal to provide any additional information and levers to convince them	Commercial operators and planners available The commercial manager could also contact the customer
(Possible in-house contracting within the purchase authorisation centre)	Offering information and simple prospects regarding product convenience	
Negotiation	Willingness to make amendments to the contracts – price negotiation	Complete standard contract Commercial operator and planner
Signing the Contract		
Product delivery	Timing in line with that established, making the customer aware of timing and willingness to provide assistance	All assembly, packaging and shipping activities are necessary

Qualitative assessment of the promotional activities

Activity	Total cost	Use of BM CED staff	Total duration	Reaching (Number - Target)
Participation in trade fairs	A	A	B	A -MS
Website	MA	B	B	A - PS
Demos	MA	MA	A	B - MS
Free test culture	A	B	A	B - MS
Adverts in specialised magazines	MA	B	MA	A - S
Public relations	MB	MB	MB	MB - S

the term “Total cost” means the total expenditure needed to perform the activity in question
the term “Use of BM CED staff” means the need to use in-house staff and the consequent impossibility to offer the activity in question through outsourcing for example

the term “Total duration” means the whole time between the start and the end of the activity in question
the term “Reaching” means the number of people or organisations reached with that activity and the type of people or organisations reached (target specifics)
A = "High", MA = "Medium-High", MB = "Medium-Low", B = "Low"; MS = "Very Specific", S = "Specific", PS = "Not Very Specific"

Promotional activity cost estimate

Activity	Cost*
Participation in trade fairs	73.000 €
Website creation	2.000 €
Website fee	1.000 €
Adverts in specialised magazines	11.000 €
Public relations**	6.200 €

** the cost refers to the performance of activities throughout the term of the business plan (5 years).*
*** in assessing this item, reference is made to the publication of scientific articles and the to the purchase of promotional material, consequently supplying a lower estimate.*
Note: the test culture and demo costs will not be explicitly calculated as these activities will be included in the broader context of the tasks assigned to the commercial staff and their cost may vary considerably depending on the type and localisation of the individual customer.

ANNEX XII – Production cycle

- **Production:** 6 working days

Core competencies of Biomicron CED are the design and assembly of the bioreactors. The actual production, envisaged from the 3rd year of business following the incorporation of the company, will be outsourced to Biomicron Srl, also based in Turin. The latter will be responsible for the transformation of raw materials and unfinished products (which it will order from its supplier network) into finished products. The delivery of these pieces will be regulated by contract and will take place within 6 working days of the order.

- **Quality control on input supplies:** 4 hours

The check to ensure that the supplies work properly and are free from defects is a particularly important activity for Biomicron CED as the bioreactor to be manufactured will be extremely delicate and precise in its measurement and stimulation of the tissue. For this reason, defective components could lead to distorted measurements and imprecisions which would convey a negative image to the company. Initially, the quality control will be managed directly by a member of the business team.

- **Assembly:** 12 hours

The assembly activity will be manual and will require the equipment used typically in a mechanical workshop. The products ordered from Biomicron Srl will be assembled with the other components (actuators, sensors, etc.). A modest sized warehouse, situated at the production premises of Biomicron Srl, will be destined for storing only those components purchased by Biomicron CED from third parties. In this way, Biomicron CED will succeed in guaranteeing its customer delivery of the product within 14 working days of receipt of the order, which corresponds to 18-20 calendar days. Alternatively, we could assess the possibility of having no stocks, for two main reasons: firstly, to avoid slow movement of stock and therefore of cash, which are hard for a company just starting up to sustain; secondly, to guarantee greater flexibility if the customer requires specific components (e.g.: of a specific brand). Naturally this option will implicate longer delivery times.

In the immediate term, it will not be necessary to employ assembly staff, because the activity will be carried out by members of the team. These will only be required later.

- **Finished product quality control:** 8 hours

The finished product quality control will implicate ensuring that all the components have been properly assembled and that there are no functional defects in the bioreactor made. Lastly, tests will be carried out on the controls and mechanical functions performed by the future assembly staff.

- **Packaging:** 3 hours

The product will be inserted into a special container that will protect it against bumps during transport by the delivery company.

ANNEX XIII – ORDER PROCESS

Actions	Working days	T=0	T=6	T=10	T=14
Acquisition of the order by the customer		X			
Issue of the order to Biomicron Srl		X			
Arrival of component to be assembled			X		
Product ready for delivery				X	
Delivery to customer					X

ANNEX XIV - INFRASTRUCTURE

RESOURCES	COST
<i>FURNISHING</i>	
Furniture	3,000 Euros
<i>TECHNOLOGICAL INFRASTRUCTURE</i>	
<i>Hardware:</i>	
- PC	1,000 Euros (x 3)
- Printer-photocopier-fax	300 Euros (x 2)
<i>Software:</i>	
- CAD/ CAM	3,000 Euros
- Website:	
Construction	2,000 Euros
Fee	200 Euros

ANNEX XV - LOCALISATION

Premises I3P

YEAR I: 11,110 €(for fee, services and activation) + 3,600 €(forfeit for use of Polytechnic premises)

YEAR II: 11,350 €(for fee and services) + 3,600 €(forfeit for use of Polytechnic premises)

YEAR III: 13,900 €(for fee and services) + 3,600 €(forfeit for use of Polytechnic premises)

At Biomicron Srl

FROM YEAR IV: 5,400 €

The decision to use premises 13P in the first few years follows careful assessment of a series of possible benefits, such as:

- *network*, i.e.: contact with new businesses, possible partners, knowledge and cooperation with companies with considerable growth prospects;
- *managerial support* which favours the launch of the business activity;
- *agreements* with professional experts.

ANNEX XVI - Sales

Table: Sales cycle

Phases/activities	Timing
Sourcing of suppliers/manufacturers	1 week
Request for information/estimate	2-3 days (also at the same time as the previous phase)
Evaluation of estimate/screening of bids	1-2 weeks
(Request for demo + demo)	0 time for request + appointment in 3-10 days + demo (1 day)
Final assessment and choice	1-2 weeks
(Possible in-house contracting within the purchase authorisation centre)	(1 week)
Negotiation	3 – 15 days
Signing the Contract	0 time
Product delivery	From the dispatch of the finished, packaged product, about 2 days in Northern Italy; 3 days to Central Italy; 4-5 days to Southern Italy and Islands; [4 days-1 week abroad]
Total time	Between 4 – 10 weeks for the most complex transactions (taking into account 1 week for production and 3 days for delivery)

ANNEX XVII - Regulation

In the European context, EC Regulation 1394/2007 is the standard, along with the other three EC Directives 2004/23, 2006/17 and 2006/86 (which regulate, among other things, the procurement, control and processes of human cells and tissues).

Propositions to improve the authorisation process for clinical studies

The process for the authorisation of drugs for gene therapy, somatic cell therapy and tissue engineering is influenced by all the limits that we already know about, connected with the complexity of the documentation to be supplied for traditional drugs, with the added weight of chronic delays in the procedure for the authorisation of study.

Considering that the new pre-clinical and clinical models, which are specific to tissue engineering, are still undergoing debate and standardisation at European and national level, it would be appropriate to:

- formalise the creation of a “pre-submission meeting” with the pertinent organisation (ISS/AIFA), which provides assistance/advice in the phase prior to presentation of the application for clinical testing, at least 6-12 months in advance;
- set up a national advisory service during the subsequent clinical development (Phases II and III). This would create a “bridge” between the proponent and the EMA/CAT which could show the company a way to carry out clinical studies and allow the Italian representatives within the CAT to report the problems encountered at local level, fitting them into a broader process of assessment.

If flanked by more efficient communication and interaction between industry and institutions, these paths could lead to greater clarity with regard to the suitability of the documentation, in support of the request for authorisation, and to the streamlining of the procedure with reduced times and costs.

Exclusions from the registration procedure (art. 28)

It is necessary for the Italian authority to define exactly the criteria and requirements according to which the products must be considered as “prepared on a non-routine basis”. Indeed, the setting of clear and objective criteria for the definition of these products would avoid the need to apply different rules to the public and private sectors, with an improper use of article 28 by certain structures, which – despite pursuing manufacturing activities within the GMP context, could manufacture products destined for human use without this implicating the obligation to have an AIC (authorisation for release for sale) issued by the EMA.

Use of drugs after the transition period

Given the current uncertainty with regard to standards and interpretation, the AIFA (Italian Drug Association) should supply clarification for drugs marketed in Italy with regard to the requirements needed to define the meaning of “legally on the market”. Furthermore, in view of the considerations already made on the reduced number of applications for AIC (authorisation for release for sale) presented, to prevent patients from being left without adequate therapy at the end of the “transitory” period, it is important for the possibility to continue using such drugs to be explicitly envisaged if there are documented activities in support of the application for authorisation for release for sale and there is no drug approved according to EC regulation 1394/2007. To this end it would be appropriate for the AIFA (Italian Drug Association) to promote this stance with the European Commission, to guarantee continuity of access to these therapies. As

well as defending patients, this would encourage companies to continue investing in the search for new therapies within the sphere of biomedicine.

Requirements for exporting to Italy

In addition to the critical issues already mentioned, the use of tissue engineering gene therapy drugs imported from EU countries should be considered. For obvious ethic and public health-related reasons, during the transitory period, these drugs should be subjected to the same criteria in terms of quality and safety already defined for those produced in Italy.

Therefore, the production of these imported drugs must be carried out in conformity to the GMP, with particular regard also to the grading of the materials and the quality of the finished products, and the AIFA (Italian Drug Association) must certify that they fall within the scope of article 29 of EC Regulation 1394/2007.

The observance of these requirements would allow doctors and patients to have the necessary guarantees for treatment.

ANNEX XVIII - Economics and Financials

INCOME
STATEMENT

Euro		Profit and Loss Time span - 5 years																	
		Year 1	Two-	Two-	Two-	Two-	Two-	Year 2	Two-	Two-	Two-	Two-	Two-	Year 3	Six-	Six-	Year 4	Six-	Year 5
		Two-	month	month	month	month	month	Two-	month	month	month	month	month	Six-	month	month	Six-	month	Six-
		period 1	period 2	period 3	period 4	period 5	period 6	period 1	period 2	period 3	period 4	period 5	period 6	period 1	period 2	period 1	period 2	period 1	period 2
SALES																			
	Product Revenues	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ 48.000	€ -	€ -	€ 48.000	€ 48.000	€ 264.000	€ 396.000	€ 726.000	€ 924.000	€ 1.584.000	€ 1.716.000
		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	Disposables	-	-	-	-	-	-	-	9,60	9,60	9,60	19,20	28,80	201,60	374,40	691,20	1.094,40	1.785,60	2.534,40
	Consulting	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	Product Development	-	-	-	9.600	9.600	9.600	5.760	5.760	5.760	5.760	5.760	5.760	27.840	33.600	57.024	91.968	151.872	216.768
		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	Total	-	-	-	9.600	9.600	9.600	5.760	53.770	5.770	5.770	53.779	53.789	292.042	429.974	783.715	1.017.062	1.737.658	1.935.302
COST OF SALES																			
	Product Costs	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ 22.110	€ -	€ -	€ 22.110	€ 22.110	€ 99.000	€ 148.500	€ 272.250	€ 346.500	€ 594.000	€ 643.500
	Variable consulting cost	€ -	€ -	€ -	€ 3.600	€ 3.600	€ 3.600	€ 2.160	€ 2.160	€ 2.160	€ 2.160	€ 2.160	€ 2.160	€ 9.960	€ 11.400	€ 18.864	€ 30.288	€ 84.432	€ 187.008
	Consulting and production staff	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ 10.200	€ 10.200	€ 10.200	€ 10.200	€ 10.200	€ 20.400
	Variable warranty costs	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ 484	€ 1.211	€ 2.543	€ 4.239	€ 6.661	€ 9.083
		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	Total	-	-	-	3.600	3.600	3.600	2.160	24.270	2.160	2.160	24.270	24.270	119.644	171.311	303.857	391.227	695.293	859.991
GROSS PROFIT		€ -	€ -	€ -	€ 6.000	€ 6.000	€ 6.000	€ 3.600	€ 29.500	€ 3.610	€ 3.610	€ 29.509	€ 29.519	€ 172.397	€ 258.663	€ 479.858	€ 625.836	€ 1.042.365	€ 1.075.311
OVERHEAD																			
	Labour cost for production and consulting	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ 10.200	€ 10.200	€ 10.200	€ 10.200	€ 10.200	€ 20.400
		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	Patent and certification maintenance cost	-	-	-	-	-	-	300	-	300	-	300	-	1.000	1.000	1.000	1.000	1.250	1.250
		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	Research and Development	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	Material	337	674	674	1.012	1.349	1.349	1.686	2.023	2.023	2.361	2.698	2.698	10.117	12.140	12.140	12.140	12.140	12.140
		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	Services	203	406	406	608	1.367	1.367	1.569	1.772	1.772	1.975	2.733	2.733	9.417	12.300	12.300	12.300	12.300	10.633
		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	Labour	322	833	1.344	1.856	2.367	2.878	3.389	3.900	4.411	4.922	5.433	5.944	22.433	27.033	27.600	27.600	27.600	27.600
		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	Total	862	1.913	2.424	3.476	5.082	5.593	6.644	7.696	8.207	9.258	10.864	11.376	41.967	51.473	52.040	52.040	52.040	50.373

Sales and Marketing																					
Marketing expenses	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€			
	-	-	-	-	2.000	800	-	1.000	16.500	500	500	1.300	18.500	1.700	18.500	1.700	18.500	11.700			
	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€			
Staff	-	-	-	-	-	-	-	-	-	-	-	-	15.000	15.000	48.000	63.000	78.000	93.000			
<i>Total</i>		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€			
		-	-	-	-	2.000	800	-	1.000	16.500	500	500	1.300	33.500	16.700	66.500	64.700	104.700			
General Administration & Finance																					
	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€			
Staff	-	-	-	-	-	-	-	-	-	-	-	-	54.000	54.000	72.000	72.000	72.000	72.000			
Outside consulting	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€			
	10.360	-	-	-	-	3.000	3.950	-	-	-	-	3.000	5.400	3.000	-	3.000	-	3.000			
	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€			
Utilities	460	460	460	460	460	460	585	585	585	585	585	585	2.000	2.000	2.351	2.651	2.951	3.251			
Rental of premises	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€			
	2.900	500	500	500	500	500	3.050	650	650	650	650	650	4.650	2.250	3.780	3.780	3.780	3.780			
<i>Total</i>		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€			
		13.720	960	960	960	960	3.960	7.585	1.235	1.235	1.235	1.235	4.235	66.050	61.250	78.131	81.431	82.031			
Total Overhead		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€			
		14.582	2.873	3.384	4.436	8.042	10.353	14.529	9.931	26.242	10.993	12.899	16.911	152.717	140.623	207.871	209.371	258.755			
EBITDA		-€	-€	-€	€	-€	-€	-€	€	-€	-€	€	€	€	€	€	€	€			
		14.582	2.873	3.384	1.564	2.042	4.353	10.929	19.569	22.632	7.383	16.610	12.608	19.680	118.040	271.987	416.464	816.557			
DEPR. & AMMORT.		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€			
		800	800	800	800	800	800	842	842	842	883	883	883	2.150	2.150	1.675	1.800	1.967			
<i>Total</i>		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€			
		800	800	800	800	800	800	842	842	842	883	883	883	2.150	2.150	1.675	1.800	1.967			
EBIT		-15.382	-3.673	-4.184	764	-2.842	-5.153	-11.771	18.727	-23.474	-8.267	15.726	11.725	17.530	115.890	270.312	414.664	814.590			
		annual aggregate										annual aggregate		2.667		133.420		684.976		1.616.517	
INTERESTS																					
EBT		-€	-€	-€	€	-€	-€	-€	€	-€	-€	€	€	€	€	€	€	€	€		
		15.382	3.673	4.184	764	2.842	5.153	11.771	18.727	23.474	8.267	15.726	11.725	17.530	115.890	270.312	414.664	801.927	814.590		
Taxes																					
Irap	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€		
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Ires	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€		
	-	-	-	229	-	-	-	5.618	-	-	-	4.718	3.517	5.259	34.767	81.093	124.399	240.578	244.377		
<i>Total</i>		€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€		
		-	-	-	229	-	-	-	5.618	-	-	4.718	3.517	5.259	34.767	81.093	124.399	240.578	244.377		
NET INCOME		-€	-€	-€	€	-€	-€	-€	€	-€	-€	€	€	€	€	€	€	€	€		
		15.382	3.673	4.184	535	2.842	5.153	11.771	13.109	23.474	8.267	11.008	8.207	12.271	81.123	189.218	290.265	561.349	570.213		

COST OF GOODS SOLD							
Full-rate production costs per unit							
Component	Quantity	Material cost	Machinery cost	Labour cost	Commercial price	Notes:	B=Biomicon, F=other suppliers
Polycarbonate culture chamber with 2 1/4" x M333 fit holes for perfusion	1	€ 1.400,00	€ 224,00	€ 214,00	€ 1.838,00	B	
Eccentric pliers for 2mm to 1mm thick scaffold made of Aisi 316L steel	2	€ 800,00	€ 188,00	€ 196,00	€ 1.184,00	B	
Culture chamber shaft coupling bellows made of medical grade silicone	2	€ 212,00	€ 14,00	€ 54,00	€ 280,00	B	
Top closed with screws incorporating 50mm petri dish with base suited to microscopic viewing, made of polycarbonate with aluminium inserts or sheet silicone with aluminium inserts	1	€ 1.300,00	€ 224,00	€ 214,00	€ 1.738,00	B	
50mm diameter petri dish	1				€ 14,00	F	
Aluminium side covers for housing silicone bellows (cf. line 4)	2	€ 95,00	€ 224,00	€ 214,00	€ 533,00	B	
Shaft for connection of pliers and adapter for Parker motor made of Aisi 316L steel (connection ensured by an Allen screw and split pin)	1	€ 95,00	€ 112,00	€ 106,00	€ 313,00	B	
Shaft for connection of pliers and adapter for charging cell made of Aisi 316L steel (connection ensured by an Allen screw and split pin)	1	€ 95,00	€ 112,00	€ 106,00	€ 313,00	B	
Adapter for connection of drive shaft made of aluminium	1	€ 54,00	€ 46,00	€ 106,00	€ 206,00	B	
Extension for connection between drive shaft and actuator adapter made of aluminium	1	€ 54,00	€ 54,00	€ 106,00	€ 214,00	B	
Adapter for connection of shaft – charge cell made of aluminium	1	€ 54,00	€ 46,00	€ 106,00	€ 206,00	B	
Adapter for connection of cell and square guide for vertical translation of charge pliers made of aluminium	1	€ 54,00	€ 54,00	€ 106,00	€ 214,00	B	
Sigma koki commercial rack & pinion translators	1				€ 253,00	F	
Igus square section runner	1				€ 121,00	F	
Custom runner housing made of aluminium	1	€ 13,00	€ 46,00	€ 106,00	€ 165,00	B	
Connection between runner housing a custom translator made of aluminium	1	€ 13,00	€ 46,00	€ 106,00	€ 165,00	B	
Sigma koki commercial screw translators	2				€ 31,00	F	
Connection between tank housing	1	€ 14,00	€ 46,00	€ 214,00	€ 274,00	B	
Custom translator made of aluminium	1	€ 14,00	€ 46,00	€ 214,00	€ 274,00	B	
Igus longitudinal positioning trolleys	2				€ 113,00	F	
Custom adaptation plates made of aluminium	2	€ 16,00	€ 46,00	€ 106,00	€ 168,00	B	
Connection profile for Igus commercial positioning trolleys made of aluminium	1				€ 91,00	F	
Auxiliary motor assembly plates made of aluminium	2	€ 54,00	€ 112,00	€ 214,00	€ 380,00	B	
Custom connection profiles made of aluminium	2	€ 32,00	€ 108,00	€ 214,00	€ 354,00	B	
Parker linear actuator complete with control driver and software	1				€ 5.360,00	F	
xftc 300 50N charge cell complete with amplifier	1				€ 990,00	F	
Case	1				€ 212,00	F	
Packaging material	1		Transport of components	Product transport	€ 50,00	F	
Overall transport costs	N		€ 90,00	€ 50,00	€ 140,00	F	
Installation and training	1				€ 50,00	F	
		total material cost	total machinery cost	total labour cost	total comm. component cost		
		€ 4.369,00	€ 1.748,00	€ 2.702,00	€ 16.244,00		
				Cost to Biomicon Srl	€ 8.819,00		
				Cost to other suppliers	€ 7.425,00		

Investments in research							
	2 years		+ VAT				
Work by entrepreneurs	70025	€ 2.917,71		€ 2.900	month		
Materials	40444	€ 5.055,50	6066,6	€ 6.070	per quarter		
Outside services	24231	€ 3.028,88	3634,7	€ 3.650	per quarter		
Hourly cost of consulting for product development	€ 140,00	(there's a margin on this)					
Hourly cost of consulting for product upgrade	€ 80,00	(no margin)					
Price of product development consulting	€ 160,00						

Labour cost

Biomicon CED has drawn up a recruitment plan for the next five years, comprising the following figures with the relative costs:

	Year 1	Year 2	Year 3	Year 4	Year 5
CFO	€ -	€ -	€ -	€ 30.000,00	€ 30.000,00
CEO	€ -	€ -	€ 20.000,00	€ 20.000,00	€ 20.000,00
CTO	€ -	€ -	€ 20.000,00	€ 20.000,00	€ 20.000,00
CMO	€ -	€ -	€ -	€ 30.000,00	€ 30.000,00
COO	€ -	€ -	€ 20.000,00	€ 20.000,00	€ 20.000,00
Research undergraduates	€ -	€ -	€ 7.500,00	€ 15.000,00	€ 15.000,00
Assemblers and “production” operators	€ -	€ -	€ 15.600,00	€ 15.600,00	€ 15.600,00
Sales staff	€ -	€ -	€ 20.500,00	€ 39.000,00	€ 83.500,00

During the first two years of life of the company, all the work will be carried out by the three business partners, while from the third year onwards, the company will invest in production operators, research undergraduates and sales staff. The wages of the latter category will increase as time goes by, because its remuneration will consist of a fixed amount plus a variable amount linked to sales (2%) to offer an incentive to work as hard as possible. From the fourth year onwards, two more figures will join the company and they will be very important to the development of the business: they are the Chief Financial Officer and the Chief Marketing Officer. The company will assign them the task of strengthening the brand on the market and planning investment strategies that will be profitable for the group.

BALANCE SHEET

Balance Sheet																			
Time span - 5 years																			
Euro	Year 1	Two-	Two-	Two-	Two-	Two-	Year 2	Two-	Two-	Two-	Two-	Two-	Year 3	Six-	Six-	Year 4	Six-	Year 5	
	Two-	month	month	month	month	month	Two-	month	month	month	month	month	Six-	month	month	Six-	month	Six-month	Six-month
	period 1	period 2	period 3	period 4	period 5	period 6	period 1	period 2	period 3	period 4	period 5	period 6	period 1	period 2	period 2	period 1	period 2	period 1	period 2

CURRENT ASSETS

Cash	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	115.345	95.465	85.305	63.516	29.956	14.316	105.460	85.368	55.905	25.159	41.105	17.572	102.361	30.120	22.864	57.361	195.474	396.566	
Inventory	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
Account	-	-	-	-	-	-	-	-	-	-	-	-	-	-	14.370	16.765	23.950	35.925	
receivables	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	-	-	-	7.680	15.360	23.040	19.968	64.896	61.824	61.824	61.824	109.824	221.456	399.344	633.373	922.256	1.447.523	1.850.109	
Total																			
Current	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
assets	115.345	95.465	85.305	71.196	45.316	37.356	125.428	150.264	117.729	86.983	102.929	127.396	323.817	429.464	670.607	996.382	1.666.947	2.282.600	

LONG TERM ASSETS

Plant	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Machinery	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
Office	3.667	3.333	3.000	2.667	2.333	2.000	2.125	1.750	1.375	1.458	1.042	625	1.875	1.125	1.250	1.250	1.500	1.500	
equipments	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	2.900	2.800	2.700	2.600	2.500	2.400	2.300	2.200	2.100	2.000	1.900	1.800	1.500	1.200	2.700	2.200	1.700	1.200	
Computers	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	6.233	5.867	5.500	5.133	4.767	4.400	4.033	3.667	3.300	2.933	2.567	2.200	1.100	-	1.500	1.200	1.733	1.267	
R&D	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	14.658	31.664	38.440	53.884	77.722	81.329	93.604	104.829	105.822	115.484	133.540	131.364	136.438	142.004	137.004	142.004	137.004	133.671	
Total LT	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
assets	27.458	43.664	49.640	64.284	87.322	90.129	102.063	112.446	112.597	121.876	139.048	135.989	140.913	144.329	142.454	146.654	141.938	137.638	

TOTAL ASSETS	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
	142.803	139.130	134.945	135.481	132.638	127.485	227.490	262.709	230.326	208.859	241.978	263.385	464.730	573.793	813.061	1.143.036	1.808.885	2.420.238	

CURRENT LIABILITIES

Short Term																			
Loans																			
Account	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
Payable	-	-	-	-	-	-	-	22.110	13.200	-	22.110	35.310	42.680	70.620	120.670	160.380	264.880	306.020	
Current																			
Portion of																			
LT Loans																			
Total																			
Current	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
Liabilities	-	-	-	-	-	-	-	22.110	13.200	-	22.110	35.310	42.680	70.620	120.670	160.380	264.880	306.020	

LONG TERM LIABILITIES

Notes																			
Payable																			
Total LT	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
Liabilities	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Total	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€	€
Liabilities	-	-	-	-	-	-	-	22.110	13.200	-	22.110	35.310	42.680	70.620	120.670	160.380	264.880	306.020	

SHAREHOLDER EQUITY	Paid-in Capital	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000	€ 10.000
	External financing	€ 148.185	€ 148.185	€ 148.185	€ 148.185	€ 148.185	€ 148.185	€ 259.962	€ 259.962	€ 259.962	€ 259.962	€ 259.962	€ 259.962	€ 441.666	€ 441.666	€ 441.666	€ 441.666	€ 441.666	€ 441.666
	Retained Earnings	-€ 15.382	-€ 19.056	-€ 23.240	-€ 22.705	-€ 25.547	-€ 30.700	-€ 42.472	-€ 29.362	-€ 52.836	-€ 61.103	-€ 50.094	-€ 41.887	-€ 29.615	-€ 51.508	-€ 240.726	-€ 530.991	-€ 1.092.339	-€ 1.662.552
	Total SH Equity & REs	€ 142.803	€ 139.130	€ 134.945	€ 135.481	€ 132.638	€ 127.485	€ 227.490	€ 240.599	€ 217.126	€ 208.859	€ 219.868	€ 228.075	€ 422.050	€ 503.173	€ 692.391	€ 982.656	€ 1.544.005	€ 2.114.218
	TOTAL LIABILITIES & SH EQUITY	€ 142.803	€ 139.130	€ 134.945	€ 135.481	€ 132.638	€ 127.485	€ 227.490	€ 262.709	€ 230.326	€ 208.859	€ 241.978	€ 263.385	€ 464.730	€ 573.793	€ 813.061	€ 1.143.036	€ 1.808.885	€ 2.420.238

[illegible]

Capital Outlays

This category includes the following items:

- Plant: this item has no value for Biomicron CED because, over the period of time envisaged, the company does not intend to purchase premises in which to pursue its activity, insofar as the registered office will be in Turin Polytechnic incubator I3P for the first three years, before moving to the premises of Biomicron Srl, where it will rent a room in which to pursue its activity.
- Machinery: this item includes all the work instruments for the production of the bioreactor
- Office Equipment: this item consists of the value of the furnishing of the premises where the company will operate.
- Computers
- R&D: this item comprises all the materials, labour and services that the company uses for research and development

The estimated amortisation plan is as follows:

- Machinery: 2 years
- Office Equipment: 5 years
- Computers: 3 years
- R&D: 3 years

The investment plan envisaged by CED, as well as the renewal of the equipment over the years due to obsolescence, is concentrated mainly on research and development; capital will be destined at the beginning of the activity and as soon as the company begins to issue invoices, thanks to sales, insofar as R&D is the key factor in this sector to continue being competitive on the market and to improve product performance.

Current Assets

The company's current assets are

- Customer Receivables: an average extension of customer payment terms will be between 90 and 120 days, due to the presence of public departments, the bureaucratic times of which will undoubtedly extend the waiting time for payments.
- Stock: evaluating that the time required to reorder materials is 6 weeks and developing the six-monthly calculation (26 weeks), the average number of reorders that the company has to prudentially cover during a six-month period with stocks of components is 4.33; calculating the reorder demand with a ratio between the amounts sold and the coverage period and reaching an average, we have calculated the average stocks and their value, multiplied by the cost of the components (7,185 €).
- Cash and cash equivalents.

Liabilities have been calculated on the basis of extended payment terms of 60 days to outside suppliers and 90 days for payment of the commercial partner Biomicron Srl.

Shareholders Equity

The items in this section are:

- Shareholders' equity: 10,000 €
- Outside Investments
- Profits reinvested.

CASH FLOW STATEMENT

Balance Sheet Time span - 5 years																					
Euro	Year 1					Year 2						Year 3				Year 4			Year 5		
	Two-month period 1	Two-month period 2	Two-month period 3	Two-month period 4	Two-month period 5	Two-month period 6	Two-month period 1	Two-month period 2	Two-month period 3	Two-month period 4	Two-month period 5	Two-month period 6	Six-month period 1	Six-month period 2	Six-month period 1	Six-month period 2	Six-month period 1	Six-month period 2	Six-month period 1	Six-month period 2	
Cash flow from Operations:																					
Net Income	-€ 15.382	-€ 3.673	-€ 4.184	€ 535	-€ 2.842	-€ 5.153	-€ 11.771	€ 13.109	-€ 23.474	-€ 8.267	€ 11.008	€ 8.207	€ 12.271	€ 81.123	€ 189.218	€ 290.265	€ 561.349	€ 570.213	€ 570.213	€ 570.213	
						-€ 30.700						-€ 11.186		€ 93.394		€ 479.483		€ 1.131.5		€ 1.131.5	
Depreciation and Amortization	€ 1.662	€ 2.713	€ 3.224	€ 4.276	€ 5.882	€ 6.393	€ 7.486	€ 8.537	€ 9.048	€ 10.141	€ 11.748	€ 12.259	€ 44.117	€ 53.623	€ 53.715	€ 53.840	€ 53.757	€ 52.340	€ 52.340	€ 52.340	
						€ 24.151						€ 59.219		€ 97.740		€ 107.555		€ 106.097		€ 106.097	
Change in Working Capital	€ -	€ -	€ -	€ 7.680	€ 7.680	€ 7.680	-€ 3.072	€ 22.818	€ 5.838	€ 13.200	-€ 22.110	€ 34.800	€ 104.262	€ 149.948	€ 198.349	€ 251.568	€ 427.952	€ 373.421	€ 373.421	€ 373.421	
						€ 23.040						€ 51.474		€ 254.210		€ 449.917		€ 801.373		€ 801.373	
Net cash provided/(used) by operating activities:	-€ 13.720	-€ 960	-€ 960	-€ 2.869	-€ 4.640	-€ 6.440	-€ 1.213	-€ 1.172	-€ 20.263	-€ 11.325	€ 44.866	-€ 14.334	-€ 47.874	-€ 15.202	€ 44.584	€ 92.537	€ 187.153	€ 249.1	€ 249.1	€ 249.1	
						-€ 29.589						-€ 3.441		-€ 63.076		€ 137.121		€ 436.285		€ 436.285	
Cash flow from Investments:																					
Purchase of equipment	29.120	18.920	9.200	18.920	28.920	9.200	19.420	18.920	9.200	19.420	28.920	9.200	49.040	57.040	51.840	58.040	49.040	48.0	48.0	48.0	
Net cash provided/(used) by investing activities:	-€ 29.120	-€ 18.920	-€ 9.200	-€ 18.920	-€ 28.920	-€ 9.200	-€ 19.420	-€ 18.920	-€ 9.200	-€ 19.420	-€ 28.920	-€ 9.200	-€ 49.040	-€ 57.040	-€ 51.840	-€ 58.040	-€ 49.040	-€ 48.0	-€ 48.0	-€ 48.0	
						-€ 114.280						-€ 105.080		-€ 106.080		-€ 109.880		-€ 97.080		-€ 97.080	
Net Cash provided/(used) by firm activities	-€ 42.840	-€ 19.880	-€ 10.160	-€ 21.789	-€ 33.560	-€ 15.640	-€ 20.633	-€ 20.092	-€ 29.463	-€ 30.745	€ 15.946	-€ 23.534	-€ 96.914	-€ 72.242	-€ 7.256	€ 34.497	€ 138.113	€ 201.0	€ 201.0	€ 201.0	
						-€ 143.869						-€ 108.521		-€ 169.156		€ 27.241		€ 339.205		€ 339.205	
Cumulated Cash Flows	-€ 42.840	-€ 62.720	-€ 72.880	-€ 94.669	-€ 128.229	-€ 143.869	-€ 164.502	-€ 184.594	-€ 214.057	-€ 244.803	-€ 228.856	-€ 252.390	-€ 349.304	-€ 421.546	-€ 428.801	-€ 394.305	-€ 256.192	-€ 55.0	-€ 55.0	-€ 55.0	
Cumulated Cash Flow (six-month period)	-€ 42.840	-€ 62.720	-€ 72.880	-€ 21.789	-€ 55.349	-€ 70.989	-€ 20.633	-€ 40.725	-€ 70.188	-€ 30.745	-€ 14.799	-€ 38.333	-€ 96.914	-€ 72.242	-€ 7.256	€ 34.497	€ 138.113	€ 201.0	€ 201.0	€ 201.0	
Cash Flow Peak (six-month period)			-€ 72.880			-€ 70.989			-€ 70.188			-€ 38.333	-€ 96.914	-€ 72.242	-€ 7.256	€ 34.497	€ 138.113	€ 201.0	€ 201.0	€ 201.0	
Cumulated Cash Flow (annual)	-€ 42.840	-€ 62.720	-€ 72.880	-€ 94.669	-€ 128.229	-€ 143.869	-€ 20.633	-€ 40.725	-€ 70.188	-€ 100.933	-€ 84.987	-€ 108.521	-€ 96.914	-€ 169.156	-€ 176.411	-€ 141.915	-€ 3.801	€ 197.2	€ 197.2	€ 197.2	
Cash Flow Peak (annual)				2		-€ 143.869						-€ 108.521						-€ 176.4	-€ 176.4	-€ 176.4	

Equity investment	€ 10.000
External Financing	€ 148.185

	€	-€	-€	-€		-€	€	-€	-€	-€	€	-€	€	-€	-€	€	€	€	
Final Net Cash Flows	115.345	19.880	10.160	21.789	-€	33.560	15.640	91.143	20.092	29.463	30.745	15.946	23.534	84.790	72.242	7.256	34.497	138.113	201.09
							€					€		€		€		€	
						cumulated	14.316					cumulated	3.256	cumulated	12.548	cumulated	27.241	cumulated	339.205

Cash Risk

Cash Flow annuali

